ARIC Manuscript Proposal #2586

PC Reviewed: 8/11/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Neural correlates of prior domain-specific cognitive decline: a voxel-based morphometry study

b. Abbreviated Title (Length 26 characters): VBM analysis of cognitive domains

2. Writing Group:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ALCS **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Data are currently available. Analyses and manuscript preparation will be performed over the next 6-12 months.

4. Rationale:

MRI correlates of cognitive impairments have been studied extensively. Most studies have focused on associations between cognitive impairments and brain volumes, globally or in pre-specified regions of interest, as was done in Knopman et al. in ARIC (1) and in other studies (2, 3). Other prior studies have focused on associations between cognitive impairments and vascular lesions (lacunes; microinfarcts; white matter hyperintensities; microbleeds) (1, 4, 5). However, less is known about the neural correlates of well-documented prior domain-specific cognitive decline.

One method that can be used to study neural correlates of cognitive function is voxel-based morphometry (VBM). VBM is a neuroimaging analysis technique that can be used to identify focal differences in gray matter (GM) or white matter (WM) density between identified groups of subjects in brain regions. Prior VBM studies looking at cognitive variables have been limited by small numbers of participants (N<100 participants) and were largely cross-sectional in design with cognition being measured only at the time of MRI (6-8), which does not distinguish poor cognition due to acquired late-life disease from that native to the individual or resulting from the individual's education or life-time social or occupational experience. Further, most studies have compared those with and without Alzheimer's disease or other types of dementia (9, 10), but little is known about comparisons among persons without dementia who have different domain-specific cognitive declines.

We propose to use VBM to identify neural correlates of prior cognitive decline over approximately 20 years in the domains of memory, language, and executive function. We expect this research to contribute to the understanding of different cognitive roles of specific brain areas.

5. Main Hypothesis/Study Question(s):

What brain regions are associated with prior domain-specific cognitive decline (memory, language, executive function) among community-living non-demented older adults in U.S. communities?

Hypotheses:
VBM will provide maps of brain regions related to declines in these specific domains, revealing affected areas that may not have been hypothesized in advance. However, there are some *a priori* hypotheses:

- Prior decline in the memory domain is associated with lower GM density in the medial temporal lobe (to include the hippocampus and entorhinal cortex) and the posterior cingulate, compared to those without prior decline in the memory domain.

- Prior decline in the language domain will be associated with lower GM density in the dominant inferior frontal gyrus and the dominant superior temporal gyrus compared to those without prior decline in the language domain.
- Prior decline in the executive function domain will be associated with lower GM density in the pre-frontal cortex, anterior cingulate, and lower GM and WM density in subcortical regions, compared to those without prior decline in the executive function domain.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Study Design**:**

Examination of neural correlates (measured at MRI in 2011-2013) of prior domain-specific cognitive declines (1990-1992 through 2011-2013).

Inclusion/Exclusion Criteria**:**

Participants who attended ARIC visit 5 (2011-2013), who were selected for a brain MRI scan, and who completed a brain MRI scan of adequate quality will be eligible for this analysis. A detailed description of the selection criteria for brain MRI at visit 5 is available in the *ARIC Neurocognitive Exam (Stages 2 and 3) Manual 17*.

Briefly, selection criteria for a brain MRI scan at visit 5 included:

1. Absence of any contraindications to MRI: cardiac pacemaker, defibrillator or valvular prosthesis, histories of meningioma, arachnoid cyst, craniotomy, with resection or radiation therapy involving the skull or brain, or normal pressure hydrocephalus, metal fragments in the eyes, brain or spinal cord, cochlear implant, spinal cord stimulator, or other internal electrical device, permanent eyeliner, or weight >350 pounds.
2. All 2004-2006 ARIC brain MRI participants (regardless of their visit 5 cognitive status).
3. All "atypical" participants (goal recruitment n~1,200), defined as either low Mini-Mental State Exam score (visit 5 MMSE <21 for whites and <19 for blacks) *or* (low visit 5 domain z-scores on 2 or more cognitive domains [domain z-score < -1.5 SD] *and* definite cognitive decline on the Delayed Word Recall Test, Digit Symbol Substitution Test, Word Fluency Test [defined as current score minus highest prior score <20th percentile on 1 or more tests or <10th percentile on 2 or more tests]).
4. A random sample of "typical" participants (those who did not meet above criteria for "atypical") (goal recruitment n~800). Sampling fractions were set for participants <80 years and ≥80 years (10% for MN, MD, and MS and 5% in NC to compensate for recruitment of brain MRI study participants).

Additionally criteria for study inclusion/exclusion are:

1. All included participants must have undergone cognitive assessment at visit 5 and at least one of the earlier visits: visit 2 (1990-1992) or visit 4 (1996-1998), or the brain MRI (2004-06).

2. Participants with an adjudicated dementia diagnosis at visit 5 (2011-2013) will be excluded.
3. Participants of non-white and non-black race will be excluded.
4. Participants of non-white race at the Washington County, Maryland and Minneapolis, Minnesota field centers will be excluded.

Exposure(s)**:**

At visits 2 and 4, three cognitive tests were performed: the Delayed Word Recall Test (DWRT), the Digit Symbol Substitution Test (DSST) and the Word Fluency Test (WFT). At visit 5, the following additional cognitive tests were performed: the Boston Naming test, the Animal Naming Test, Logical Memory I and II, Incidental Learning, and the Trail Making Test Parts A and B. At the Brain MRI visit DWRT-Recognition and the Stroop test were also performed.

The DWRT (11) is a test of verbal learning and recent memory. In this test, participants were given 10 common nouns that they were asked to learn by using each word in one or two sentences. After a five-minute delay, participants were given 60 seconds to recall the words. The score for the DWRT is the number of words correctly recalled. DWRT-Recognition (12) uses the same 10 common nouns in the DWRT and uses the same protocol to have participants learn the words. After a five-minute delay, participants were asked to identify the noun that was previously learned out of four choices. The score for DWRT-recognition is the number of words correctly identified.

The DSST of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (13) is a test of executive function and processing speed, where participants were asked to translate numbers to symbols using a key. The score is the total number of numbers correctly translated to symbols within 90-seconds and the range of possible scores is 0 to 93.

The WFT, also known as the Controlled Oral Word Association Test (COWA) of the Multilingual Aphasia Examination (14), is a test of executive function and language, and test's one's ability to spontaneously generate words beginning with a particular letter, excluding proper names or places. Participants were given 60 seconds for each of three trails for the letters "F", "A", and "S". The word fluency score is the total number of words generated across the three trials.

The Boston Naming Test (15) is a visual confrontational naming test that tests one's ability to verbally name pictures of common objects. Participants were given 20-seconds to name each object. The score is the total number correct and the range of possible scores is 0 to 60.

Animal Naming (16) is a test of semantic category fluency in which the participant is asked to spontaneously generate words from a specific category (in this test, animals). Participants could name multiple words in the same subcategory (e.g., dog, golden retriever, German shepherd). The score is the total number of animals generated within 60 seconds.

The Logical memory test, from the Wechsler Memory Scale-Revised (WMS-R) (17) is a test of immediate (LM I) and delayed (LM II) memory. In this test, two short stories are presented, each

containing a total of 25 pieces of information. Immediately after each story is presented, free recall of the story is elicited and the score for LM I is the total number of pieces of information recalled. After a 30-minute delay, free recall of both stories is elicited and the total number of pieces of information recalled at this time comprises the score for LM II.

The Incidental Learning Test (18) is a test of memory in which the participant is given 60-seconds to record as many symbols from the previously administered DSST as he/she can remember. The participant is then given 60-seconds to fill in the numbers that go with each symbol. The score is the total number of symbols and digit-symbol pairs that are correct.

TMT-A (19) is primarily a test of processing speed in which participants are asked to draw consecutive lines from the numbers 1 to 25 as fast as possible. The score is the time (in seconds) for completion of this task, with a maximum alotted time of 240 seconds.

TMT-B (19) is a test of executive function and processing speed in which participants are asked to draw consecutive lines alternating between the numbers 1 to 13 and the letters A to L. The score is the time (in seconds) for completion of this task, with a maximum allotted time of 240 seconds.

The Stroop test (20) is a test of executive function and is comprised of three subtests: Color Naming, Word Reading, and Interference. During the Color Naming subtest, individuals are instructed to name the color of rectangles. The Word Reading subtest requires participants to read words printed in black ink. The Interference subtest consists of words printed in an incongruous ink color (e.g., the word "green" printed in blue ink). Participants are required to inhibit the automatic tendency to read the words, and are asked name the color of the ink for each word. The score is the number correct for each subtest.

Using latent variable analyses, the cognitive tests have previously been grouped into domains (see Gross *in press* Epidemiology):

1. Memory: DWRT, DWRT-Recognition, Logical Memory I and II, Incidental Learning
2. Language: WFT, Boston Naming, Animal Naming
3. Executive Function: DSST, Trail Making Test Parts A and B, Stroop.

Using methods described below in the data analysis section of the proposal, we will create eight groups defined by the presence or absence of domain specific cognitive decline defined using data from visit 2 (1990-1992), visit 4 (1996-1998), and visit 5 (2011-2013).

The following table defines each of the eight groups:

Category		**Memory**	**Language**	**Executive Function**
1	No Decline	-	-	-
2	Decline in Memory Only	DECLINE	-	-
3	Decline in Language Only	-	DECLINE	-
4	Decline in Executive Function Only	-	-	DECLINE
5	Decline in Memory and Language	DECLINE	DECLINE	-

6	Decline in Memory and Executive Function	DECLINE	-	DECLINE
7	Decline in Language and Executive Function	-	DECLINE	DECLINE
8	Decline in All Domains	DECLINE	DECLINE	DECLINE

* Decline versus no decline will be defined using percentiles (see data analysis section)

Preliminary analyses suggest that if a cut-point of the 20th percentile for decline versus no decline, the following numbers of participants in each category will be observed:

Category		**Number**
1	No Decline	1122
2	Decline in Memory Only	162
3	Decline in Language Only	137
4	Decline in Executive Function Only	136
5	Decline in Memory and Language	57
6	Decline in Memory and Executive Function	59
7	Decline in Language and Executive Function	85
8	Decline in All Domains	88

If a cut-point of the 40th percentile for decline versus no decline, the following numbers of participants in each category will be observed:

Category		**Number**
1	No Decline	658
2	Decline in Memory Only	196
3	Decline in Language Only	141
4	Decline in Executive Function Only	145
5	Decline in Memory and Language	116
6	Decline in Memory and Executive Function	112
7	Decline in Language and Executive Function	165
8	Decline in All Domains	313

To assess the robustness of the domains to differing numbers of cognitive tests performed at each visit, we will perform a sensitivity analysis among those with cognitive test data at both the Brain MRI visit (2005-2006) and at visit 5 (2011-2013) because at these two visits, comprehensive neuropsychologial batteries were performed (versus just the DWRT, DSST, and WFT at visits 2 and 4).

We will perform 9 comparisons between groups:

1. Group 1 (No decline) versus Group 2 (Decline in memory only)
2. Group 1 (No decline) versus Group 3 (Decline in language only)
3. Group 1 (No decline) versus Group 2 (Decline in executive function only)
4. Group 1 (No decline) versus Groups 2+5+6+8 (Any decline in memory)
5. Group 1 (No decline) versus Groups 3+5+7+8 (Any decline in language)
6. Group 1 (No decline) versus Groups 4+6+7+8 (Any decline in executive function)
7. Groups 1+3+4+7 (No decline in memory) versus Groups 2+5+6+8 (Any decline in memory)

8. Groups 1+2+4+6 (No decline in language) versus Groups 3+5+7+8 (Any decline in language)
9. Groups 1+2+3+5 (No decline in executive function) versus Groups 4+6+7+8 (Any decline in executive function)

Outcome(s):

A detailed description of the visit 5 brain MRI protocol is available in the *ARIC NCS MRI Manual 13*. Briefly, visit 5 brain MRI scans (2011-2013) were performed using 3 Tesla scanners (MN: Siemens Trio [vb17 software]; MD: Siemens Verio [vb17 software]; MS: Siemens Skyra [D13 software]; NC: Siemens Skyra [D11 software]. The following sequences were obtained: Localizer, MP-RAGE (1.2 mm slices), Axial T2*GRE (4 mm slices), Axial T2 FLAIR (5 mm slices), Field Mapping (3 mm slices), Axial DTI (2.7 mm slices for Skyra and Verio scanners and 3 mm slices for Trio scanners).

Briefly, VBM involves the following pre-analysis steps (21-23):
Each T1 scan gets a geometric correction applied for gradient distortions, as well as an intensity correction to remove inhomogeneity bias. Next the corrected scans are segmented and spatially normalized using the Unified Segmentation approach in SPM5. The segmented, spatially normalized GM and WM images are then modulated to correct for stretching and compression induced by the spatial normalization. Finally the modulated normalized WM and GM images are smoothed with a Gaussian smoothing filter.

We will enter these pre-processed images into the general linear model framework of SPM to produce voxel-wise GM and WM tissue density differences among the groups described in the above exposures section.

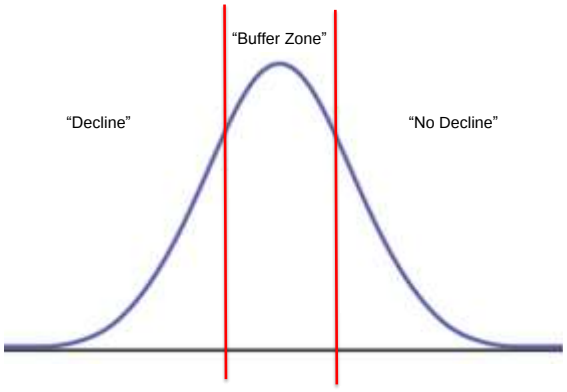
Data Analysis**:**

To define each of our exposure groups, we will use mixed models with random intercept and slope to model cognitive trajectories over approximately 20-years using latent variables for cognitive domains (see MSP 2215 for methods details) from visit 2 (1990-1992), visit 4 (1996-1998), and visit 5 (2011-2013). The models will be adjusted for age (years, continuous) and race (white; black). Using these models, we will define cut-points for "decline" versus "no-decline" for each domain based on percentiles of the best linear unbiased predictions (BLUPs). We will also run VBM regression analyses using the continuous valued latent variables for each cognitive domain rather than grouping the subjects into bins based on cut-points in the domain scores. We will also consider cross-sectional analyses using visit 5 test scores.

Each of the 8 decline groups will be characterized by visit age, sex, and race at visit 2, APOE ε4 genotype, education, race, visit 2 DWRT, DSST and WFT scores (crude and Z-scores), visit 5 domain Z-scores, and visit 5 cognitive status (normal or MCI) and, for those with MCI, etiology (AD, vascular, mixed, other).

We will enter these pre-processed images into the general linear model framework of SPM to produce voxel-wise T-test maps among the groups described in the above exposures section.

As a sensitivity analysis, we will redefine our "decline" versus "no decline" group definition. We will add a "buffer zone" comprised of excluded participants whose scores are in between the groups of "decline" versus "no decline" for each domain (versus just using one cut-point for "decline" versus "no decline"). This analysis will serve to highlight the extremes in our population.



Limitations:
We will be relating prior trajectories of cognitive function to MRI data in older age. Although brain MRIs have now been performed on a subset of ARIC participants at three time points (1993-1995, 2004-2006, 2011-2013), we will not be performing analyses of change in MRI variables over time. The brain MRIs performed in 1993-1995 and 2004-1006 were only performed in North Carolina and Mississippi. Additionally, brain MRIs performed in 1993-1995

and 2004-2006 were performed on 1.5 Tesla scanners, while the brain MRIs performed at visit 5 were performed on 3 Tesla scanners.

7.a. Will the data be used for non-CVD analysis in this manuscript?
___ Yes __X__ No

7.b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?
____ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes __X__ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php
__X__ Yes ___ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

MSP 314: "Cerebral abnormalities identified on magnetic resonance imaging and cognitive functioning: the ARIC Study" (Thomas Mosley)

MSP 1119: "MRI predictors of global and domain specific cognitive function at 10 years follow-up: the ARIC MRI Study" (Laura Coker)

MSP 1771: "Cognitive, vascular risk factor, and APOE genotype predictors of hippocampal volume" (David Knopman)

MSP 2215: "Development of longitudinal measures of general and domain-specific latent factors for cognitive performance (Alden Gross)

MSP 2288: "Associations of brain imaging with cognitive change over 20 years" (David Knopman)

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal:

__X__A. primarily the result of an ancillary study (list number*):
ARIC Brain MRI 1999.01 and ARIC NCS 2008.06

____ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)*)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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